Models to Estimate Hazard to Humans and the Environment

The HAZARD MODELS included in this section are:

- OncoLogic
- ECOSAR
- Screening for Non-Cancer Human Health Effects (not a computerized model, but a step-wise screening protocol)
- PBT Profiler

Following are brief fact sheets providing information on the models OPPT has developed and uses to estimate environmental fate of chemicals. Information provided on each model includes:

- What hazard endpoint does the model estimate?
- What is significant about the hazard endpoint to risk assessment?
- Why is knowing hazard properties important?
- Why would I want to use the model?
- What do I need to run the model?
- What are the inputs and outputs for the model?

OncoLogic to Estimate Potential Carcinogenicity

What Does the OncoLogic Model Do?

OncoLogic estimates the potential for a chemical to cause cancer in humans using the known carcinogenicity of chemicals with similar chemical structures, information on mechanisms of action, short-term predictive tests, epidemiological studies, and expert judgment. OncoLogic can tell the risk assessor the potential for the chemical to cause cancer in humans (carcinogenicity) and help the assessor determine if further testing of the chemical (bioassays) may be advisable.

How are the model predictions useful in risk assessment?

An understanding of the potential for the chemical to cause cancer helps the risk assessor estimate the impact of the release of that chemical on the surrounding human population.

Inputs

- Class of chemical (fiber, polymer, metal, or organic compound)
- Chemical structure
- Functional groups present
- Additional properties listed in Flow Diagrams for each module.

Outputs

- Summary of predicted concern level (high to low)
- Line of reasoning for estimation

Important Notes

OncoLogic users need: Good understanding of organic chemistry; Chemical class of the compound; Certain physical and chemical properties of the compound

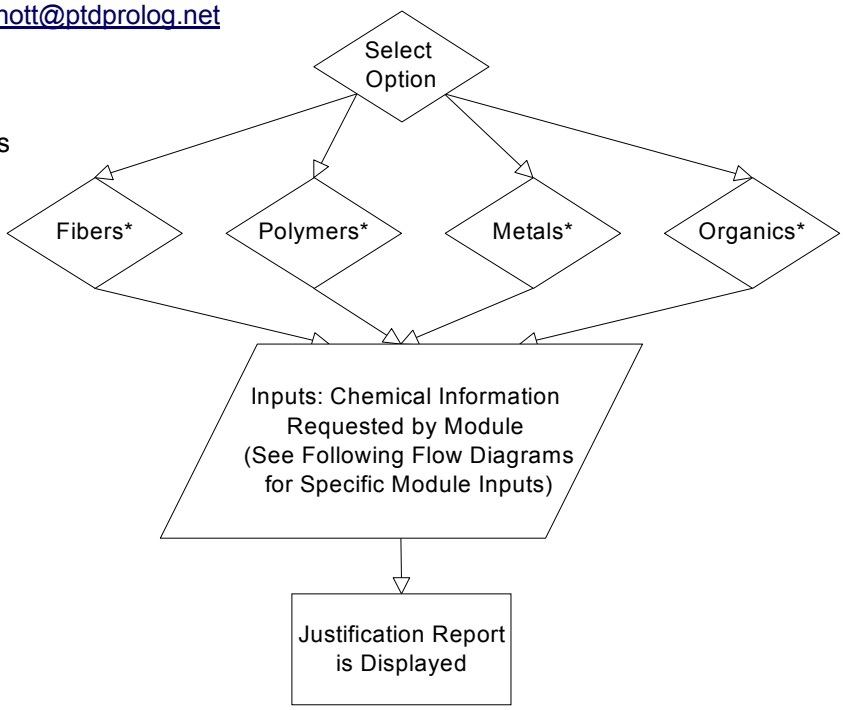
OncoLogic has modules to estimate carcinogenicity of 4 types of compounds: (1) Fibers, (2) Metals, (3) Polymers, and (4) Organics

Where Can I Get OncoLogic?

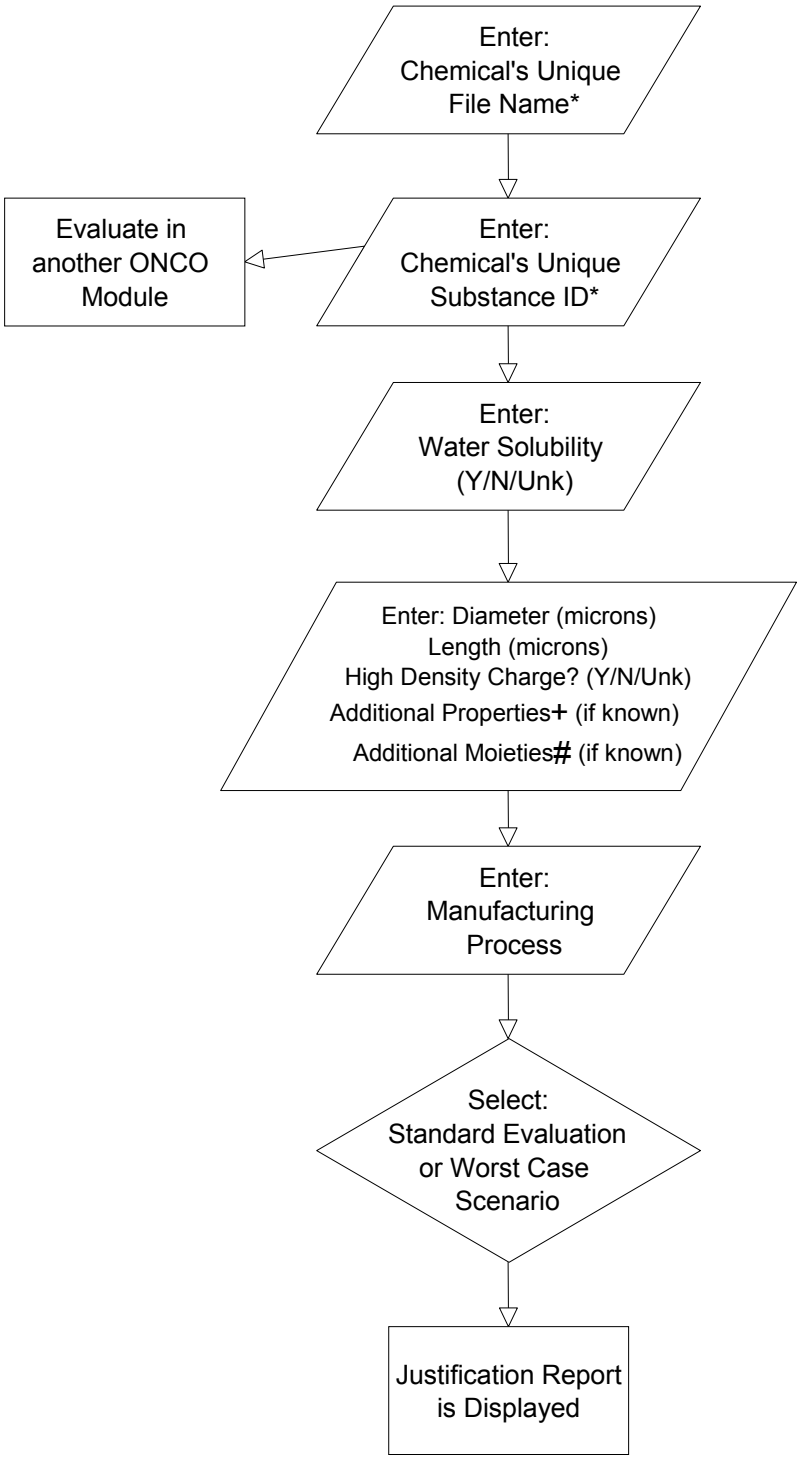
OncoLogic, developed by LogiChem under a cooperative agreement with USEPA, OPPT in support of Sec. 5 of TSCA, can be obtained by contacting: Marilyn S. Arnott, Ph.D., LogiChem, Inc., PO Box 622, Narberth, PA 19072, Email: marnott@ptdprolog.net

Using OncoLogic

Shown on the right is a Flow Diagram for OncoLogic. Each of the 4 modules shown has a detailed flow diagram which is presented on the following pages.



OncoLogic Model Flow Diagram - Fibers



Inputs Needed for Fibers Evaluation:

Water solubility (yes/no)

Diameter (microns)

Length (microns)

Additional Inputs Needed for Refining the Evaluation Are:

Presence of electrical charge

Properties

- Flexibility
- Durability
- In vivo biodegradability
- Surface characteristics
- Splitting properties

Moieties

- High molecular weight polymer
- Low molecular weight organic moiety
- Metals or metalloids

Manufacturing process

Use scenario

*NOTE: The chemical's file name and substance ID are unique names that the user enters. The chemical's file name is limited to 8 characters. The program will take up to 240 characters for the chemical's substance ID.

Sample Output from OncoLogic Fibers Justification Report

INPUTS:

Chemical file name	=	Fiber1	High density charge	=	Unk
Substance Id	=	Fiber1			
Additional properties:					
Water soluble	=	No	Durability	√	
Diameter	=	0.1 - 0.5 microns			
Moieties	=	none	Median(s)	=	0
Manufacturing process	=	Crystallization	Length	=	1 - 3 microns
Scenario evaluation	=	Standard	Aspect ratio	=	0

Justification Report is saved in ONCO dir. as ASCII file as "Chemical file name.JST"

RESULTS:

SUMMARY:

Code Number: Fiber1

Substance Id: Fiber1

The final level of this fiber-type substance is HIGH.

JUSTIFICATION:

STANDARD EVALUATION

The unifying concept of fiber carcinogenisis is the Stanton Hypothesis. This hypothesis states that the dimensions of a fiber are the major criteria for establishing the concern for its *carcinogenic* potential.

The STANDARD evaluation is the accepted method for determining the *carcinogenic* potential of a fiber. It is based on the median diameter and length. The distribution of dimensions is assumed to be uniform. When a range is entered, the program calculates the median as the average of the high and low values.

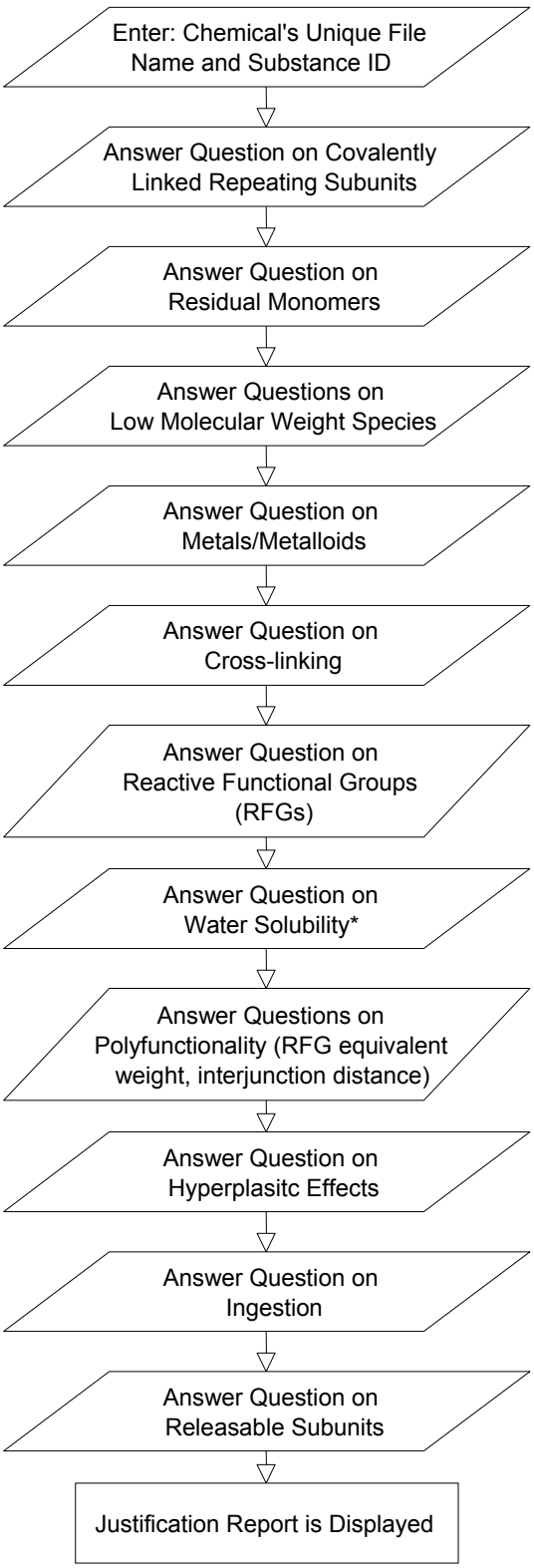
Since the diameter of the fiber is equal to or greater than 0.25 microns and less than 1.5 microns, and its aspect ratio is greater than 5 and not more than 32, the initial level of concern for *carcinogenic* potential of this fiber is MODERATE.

Naturally occurring fibers and synthetic fibers that are manufactured through a crystallization process are assumed to have strong electron donor/basic sites on their surface, since these conditions provide time for orderly build-up of surface structure. This increases the level of concern to HIGH-MODERATE.

The fiber exhibits the following property or properties: durability. These characteristics make minor modifications to the concern level and many are inter-related. Thus, regardless of the number of these characteristics the fiber exhibits, the final level of concern is increased by only one step to HIGH.

The final concern for this fiber-type substance is HIGH.

OncoLogic Model Flow Diagram - Polymers



Inputs Needed for Polymers Evaluation:

Molecular weight

Water solubility and behavior in water

Polyfunctional behavior

Hyperplastic effects

Possible Ingestion

Information on chemical structure/properties, including presence of:

- Covalently-linked units
- Residual monomer
- Residual functional groups
- Low molecular weight species
- Metals or metalloids
- Cross-linkages
- Reactive functional groups
- Internal releasable subunits
- Terminal/pendant releasable subunits

*If water solubility is in ppm, convert to percent by dividing the number by 10,000. If water solubility is unknown, enter 0.

Sample Output from OncoLogic Polymers Justification Report

INPUTS:

Chemical file name	=	Polymer1
Substance Id	=	Polymer substance A
Molecular weight	=	1,100
Covalently linked units	=	Yes
Residual monomers >2%	=	No
Low MW species (<500) present	=	Yes
Polymer reactive functional groups (RFGs)	=	Yes
RFGs present	=	Oxygen
Oxygen RFG	=	Epoxide (unsubstituted)
Additional RFGs present	=	No
Metals/Metalloids present	=	No
Crosslinkages present	=	No
Polymer RFGs present	=	Yes
Identify Polymer RFG	=	Oxygen
Oxygen RFG	=	Epoxide (unsubstituted)
Additional RFGs present	=	No
Water solubility as percent weight	=	0.2
Polyfunctional	=	Yes
Functional groups equivalent. wt.	=	550
Interjunction distance	=	Yes
Hyperplastic effects	=	No
Absorption into soft tissue	=	Unknown
Ingestion possible	=	Yes
Internal release subunits	=	No
Terminal pendant subunits	=	No

Justification Report is saved in ONCO directory as ASCII file as “Chemical file name.JST”

RESULTS:

SUMMARY:

CODE NUMBER: polymer1

SUBSTANCE ID: polymer substance A

The final level of *carcinogenicity* concern for this polymer is LOW MODERATE.

Based on the reactive functional group Epoxide (unsubstituted), the level of concern for the low molecular weight species LOW MODERATE.

CAUTIONARY NOTES:

1. Plasticizers and other additives, if present, should be evaluated separately in the Organics Subsystem.

2. Counterions of polymers with ionic backbones should be evaluated separately.

Continued on next page

Sample Output from OncoLogic Polymers Justification Report

Continued from previous page

JUSTIFICATION:

Because the substance consists of covalently linked repeating units and has a molecular weight greater than or equal to 1000, the substance is classified as a high molecular weight polymer.

Since the polymer contains less than 2% residual monomer(s), the *carcinogenicity* concern for any residual monomers is LOW.

The polymer contains low molecular weight species (>2% below 500), with a reactive-functional-group-bearing sidechain. The level of *carcinogenicity* concern for the low molecular weight species is based on the reactive functional group: Epoxide (unsubstituted).

The level of *carcinogenicity* concern for the low molecular weight species is LOW MODERATE.

The polymer is not cross-linked.

Since the percent water solubility is greater than or equal to 0.1%, the polymer is considered to be soluble in water.

The reactive functional group (RFG) which was used during the evaluation of the polymer is: Epoxide (unsubstituted).

This water soluble polymer is polyfunctional. Based on the expert-assigned inherent *carcinogenic* potential of the RFG(s) that you have entered and the entered information on the functional group equivalent weight of 550 daltons, which is low enough to cause concern, and the interjunction distance of less than ten atoms, which is within the favorable distance for potential cross-linking, the RFG which is retained for the evaluation of the polymer is Epoxide (unsubstituted).

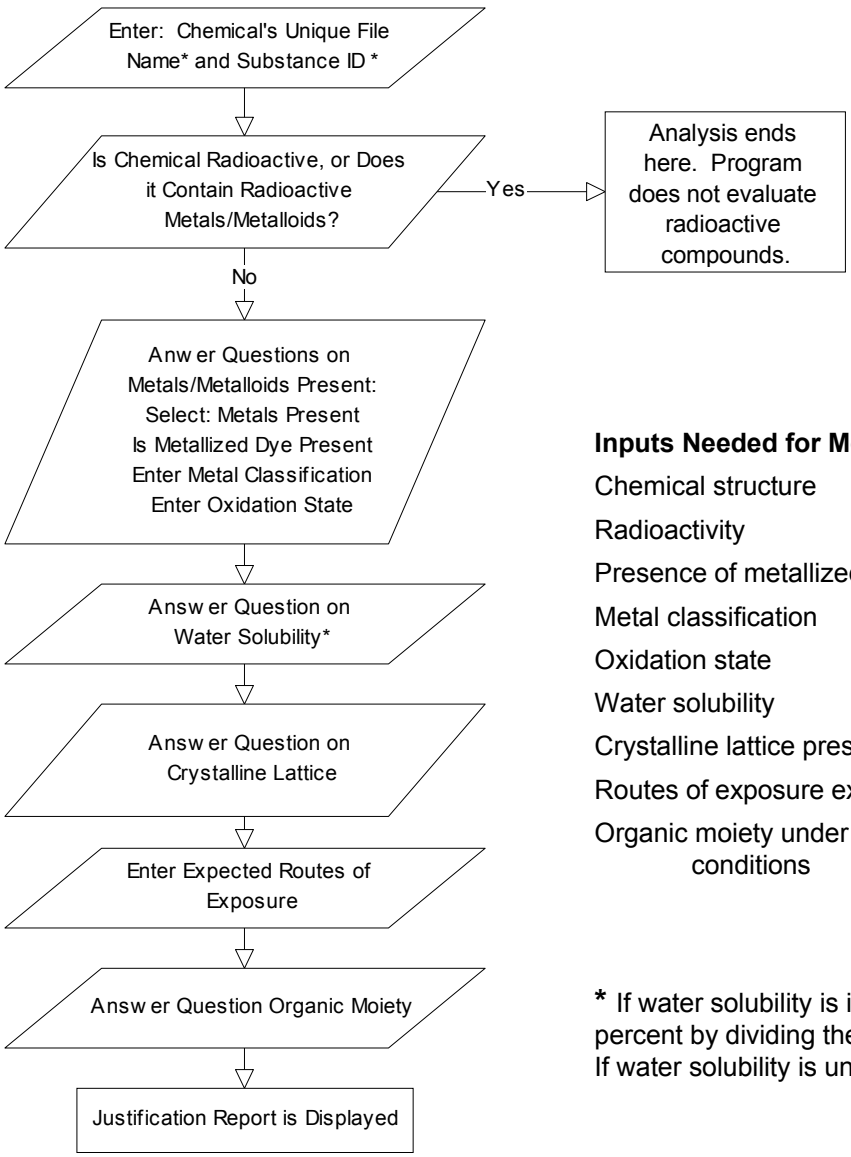
Since this polymer has been demonstrated not to cause (or is not known to have caused) inflammatory and/or hyperplastic changes, *carcinogenicity* concerns arising from these pathophysiological changes can be eliminated.

The RFG which is contained in this polymer is known to be stable in solution or as an emulsion in water. The current level of *carcinogenicity* concern based on the RFG is retained.

The water soluble polymer has a molecular weight less than or equal to 5,000. The polymer contains reactive-functional-group-bearing sidechains but has not (or is not known to have) demonstrated an ability to be absorbed and to accumulate in soft tissue. Therefore, the level of *carcinogenicity* concern for this polymer is LOW MODERATE.

The final concern for this polymer is LOW MODERATE.

OncoLogic Model Flow Diagram - Metals



Inputs Needed for Metals Evaluation:

Chemical structure

Radioactivity

Presence of metallized dye or pigment

Metal classification

Oxidation state

Water solubility

Crystalline lattice present?

Routes of exposure expected

Organic moiety under physiological conditions

***** If water solubility is in ppm, convert to percent by dividing the number by 10,000. If water solubility is unknown, enter 0.

Sample Output from OncoLogic Metals Justification Report

INPUTS:

Chemical file name	=	Crystal	Oxidation state	=	Hexavalent
Substance Id	=	Crystal	Water solubility	=	Sparingly soluble
Radioactivity	=	No	Crystalline lattice	=	Yes
Metals present	=	Cr and Zr	Route of exposure	=	Inhalation
Metallized dye or pigment	=	No	Organic *moiety*	=	No
Metal classification	=	Inorganic or other comp.			

Justification Report is saved in ONCO directory as ASCII file as "Chemical file name.JST"

RESULTS:

Code Number: crystal
Substance Id: crystal

SUMMARY:

The final level of concern for this Cr-containing inorganic or organic compound, when the anticipated exposure is via the inhalation route, is HIGH.

JUSTIFICATION:

Since this substance contains more than one metal, Cr, Zr, the system has considered all metals present. The level of concern and the line of reasoning are based on the metal which provides the highest level of *carcinogenicity* concern. When more than one metal gives the same highest level of concern, the line of reasoning is given for only one of the metals.

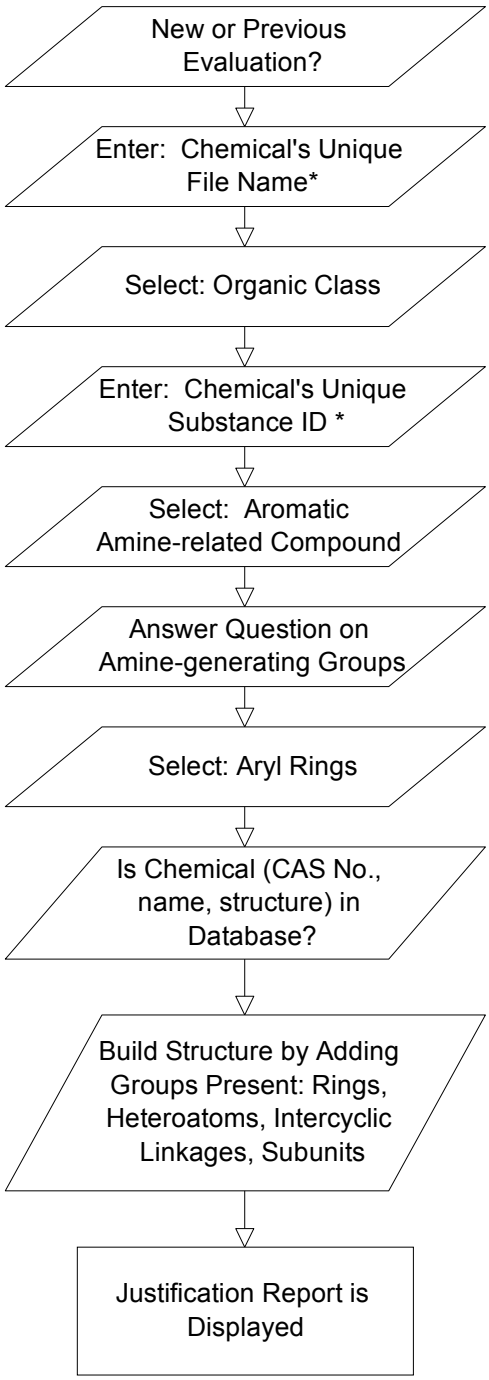
In general, virtually all Cr-containing compounds are of some *carcinogenicity* concern unless they can be clearly shown to be not bioavailable. Exposure to these compounds by inhalation or injection is of greater concern than exposure by the oral or dermal route.

The *carcinogenic* potential of inorganic chromium compounds is affected by their oxidation state, crystallinity, and solubility, which affect the extent of compound uptake by cells. Hexavalent compounds are more easily taken up by cells than trivalent; and crystalline compounds are more easily taken up than amorphous compounds. Sparingly soluble and insoluble compounds are more likely than soluble compounds to be retained at the site of exposure, and thus have more of an opportunity to be taken up by the cells. Organic chromium compounds containing a Cr-C covalent bond are treated as inorganic compounds because the Cr-C covalent bond is expected to be easily hydrolyzed in aqueous solution.

Since the substance is a(an) inorganic or organic compound, and the oxidation state of chromium is hexavalent, and exposure to this sparingly soluble, crystalline substance is expected to be by the inhalation route, the level of *carcinogenicity* concern is HIGH.

The final level of concern for this Cr-containing inorganic or organic compound, when the anticipated exposure is via the inhalation route, is HIGH.

OncoLogic Model Flow Diagram - Organics



Inputs Needed for Organics Evaluation:

Organic chemical class

CAS number/Chemical name (if listed)

Molecular structure, including presence of:

- Rings
- Functional groups
- Linkages
- Substituents

NOTE:
*The chemical's file name and substance ID are unique names that the user enters. The chemical's file name is limited to 8 characters. The program will take up to 240 characters for the chemical's substance ID.

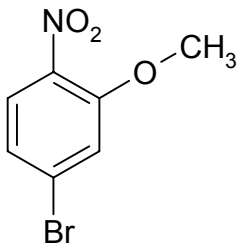
Sample Output from OncoLogic Organics Justification Report

INPUTS:

Chemical file name = Amine1
Organic class = Aromatic amine
Substance Id = Aromatic amine#1
Aromatic-related compound class = None
Amine-generating group = Yes
Aryl rings selected:
6-member rings = 1
Heteroatoms = No
Answers are correct

Structure building:
Select:
- Build
- Add
- Substituents
- Alkoxy ($-OCH_3$)
- Amine-generating group (NO_3)
- Other (Br)

RESULTS:



Justification Report is saved in ONCO directory as ASCII file as "Chemical file name.JST"

SUMMARY

Code Number: Amine1 Substance Id: Aromatic Amine#1

The level of carcinogenicity concern for this compound is HIGH-MODERATE.

JUSTIFICATION:

In general, the level of carcinogenicity concern of an aromatic amine is determined by considering the number or rings, the presence or absence of heteroatoms in the rings; the number and position of amino groups; the nature, number and position of other nitrogen-containing 'amine-generating groups;" and the type, number and position of additional substituents.

Aromatic amine compounds are expected to be metabolized to N-hydroxylated/N-acetylated derivatives which are subject to further bioactivation, producing electrophilic reactive intermediates that are capable of interaction with cellular nucleophiles (such as DNA) to initiate carcinogenesis.

Nitro groups of aryl compounds can be reduced by nitro reductase to amino groups yielding aromatic amine compounds. The evaluation of this compound proceeds as if the nitro group were a free amine group.

An aromatic compound containing one benzene ring, one amino group, and one methyl or methoxy group ortho- to the amino group, has a carcinogenicity concern of HIGH-MODERATE.

The additional chloro and/or bromo group(s) generally raise(s) the level of concern, but they also impose an upper limit of HIGH-MODERATE on the concern level of the compound. Therefore, the level of concern remains HIGH-MODERATE.

The final level of carcinogenicity concern for this compound is HIGH-MODERATE.

Screening for Non-cancer Human Health Effects in the Absence of Data

The P2 Framework models predict aquatic hazard (ECOSAR and the PBT Profiler), cancer hazard potential of chemicals (OncoLogic), and identify structures present described in EPA's Chemical Categories (PBT Profiler). As currently constructed, the does not address all biological endpoints. The "Screening for Non-cancer Human Health Effects" protocol is provided as one method for screening chemicals of concern for non-cancer health effects in the absence of data. The protocol adheres to the scientifically accepted data hierarchy, and follows that used by EPA's Risk Assessment Division in the estimation of non-cancer health effects of PreManufacture Notices (PMNs) under TSCA. As described in an earlier section of this manual, EPA has more than 20 years experience reviewing chemicals in the absence of data.

Data Hierarchy

★ ★ ★ Highest Quality: Validated measured data from a well designed laboratory study are always preferred.

★ ★ Analog Data: When data are not available, data on a close analog may be used. Analog must be identified by a qualified chemist.

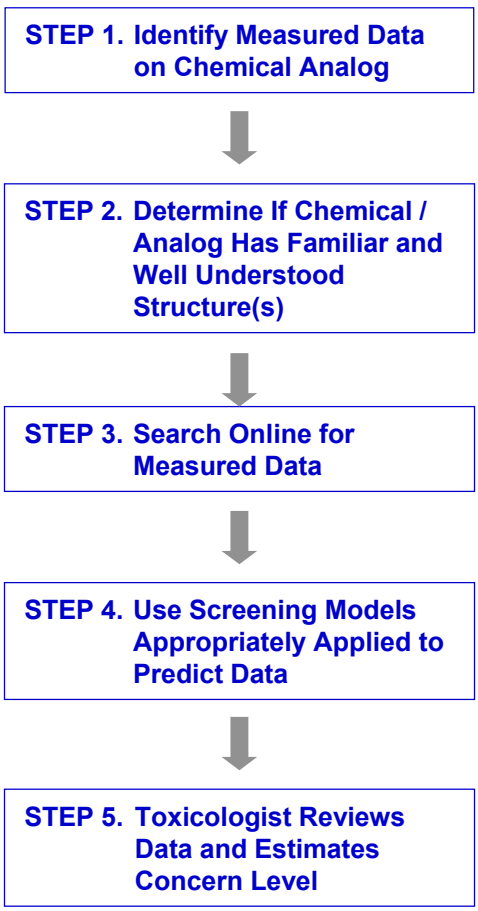
★ Predicted Data: If no data on the chemical or the analog can be located, data may be predicted by appropriately using scientifically sound models.

If Testing Becomes Necessary

If measured data are not available, predictive models can not be used, and a decision is made to conduct testing, the screening process described here can help identify the most relevant properties, effects, and exposures, and help determine which tests may be necessary to fully characterize the chemical(s). When deciding on testing, or reviewing test data, consideration should be given to the test species, route of exposure, and quality of the data. Information on these aspects can be found in OPPTS' harmonized test guidelines developed for testing chemicals under TSCA and Federal Insecticide and Rodenticide Act (FIFRA) www.epa.gov/opptsfrs/home/testmeth.htm Relevant guidelines include: #835 (Fate, Transport and Transformation), #850 (Ecological Effects), #870 (Health Effects), and 880 (Biochemicals). Additional reliable test guidelines are the Organization for Economic Cooperation and Development (OECD) Screening Information Data Sets (SIDS), which are described at www1.oecd.org/ehs/guide/index.htm and www.epa.gov/chemrtk/sidsappb.htm. When characterizing potential risk of the chemical of concern, EPA's Risk Assessment Guidelines (located at http://www.epa.gov/ncea/rafpub.htm) can provide information on assessing risk.

Screening for Non-cancer Human Health Effects

The steps in this protocol are illustrated to the right.



Screening for Non-cancer Human Health Effects in the Absence of Data

STEP 1. Locate Measured Data on Chemical / Analog

Data on the following properties should be located. Suggested data sources are included in Appendix B of this document.

- Physical / Chemical Properties
- Fate Properties
  - Biodegradation
  - Media half-lives
  - Metabolites/break down products
- Biochemical Transformation Potential
  - Reaction intermediates or reaction products
- For Polymers
  - Number average molecular weight
  - % below MW of 500 and % below MW of 1,000
  - MW distribution, if available
- For Surfactants
  - Cmc and Krafft temperature (ambient conditions)
- For Solids
  - Particle size distribution
  - Melting point
- Aquatic Toxicity: Chronic and acute toxicity to fish, invertebrates, algae

STEP 2. Determine If Chemical / Analog Has Familiar and Well Understood Structure(s)

- Check whether chemical belongs to one of EPA's New Chemicals Program Chemical Categories, available at www.epa.gov/oppt/newchems/chemcat.htm
- Chemicals Causing Local Effects are listed in Appendix D. Chemicals Causing Systemic Effects are listed in Appendix E. (Lists are not intended to be exhaustive.)
- Polymers (high MW chemicals) may not be toxic to fish as they are often too large to cross most biological membranes, however certain types of polymers may present human health concerns. EPA has concern for three types of polymers with MW >10,000. These are (a) soluble, (b) insoluble/non-water absorbing ("non-swellable"), and (c) water absorbing ("swellable"), describes at www.epa.gov/opptintr/newchems/hmwtpoly.htm) and included in Appendix F.

STEP 3. Search Online for Measured Data

Measured data may be available in reference or online sources. The source of any data submitted should be provided. The test species and test quality should considered as well. There are many reference and online sources of human health effects data. Appendix B provides reference and online data sources, however, these lists are not intended to be exhaustive. Readers are encouraged to conduct their own online searches.

STEP 4. Use Screening Models, Appropriately Applied, to Predict Data

Many screening models are available that predict human health effects. One online aid to identifying appropriate models that predict the desired endpoints is OECD's Database on Chemical Risk Assessment Models at http://webdomino1.oecd.org/comnet/env/models.nsf.

Before any screening model is used, it is essential that the assessor determine the appropriateness of that specific model for evaluating the chemical(s) of concern. Not all models can evaluate all classes of chemicals. In addition, model results must be interpreted with caution. Consult the specific model's User Guide for information on appropriately using the model, and always provide the specific model used to predict the properties and effects submitted.

Once the appropriate models have been identified, and the chemical has been evaluated, the predictions should be evaluated carefully. Once this has been done, the assessor can summarize the significance of potential hazards.

Screening for Non-cancer Human Health Effects in the Absence of Data

STEP 5. Toxicologist Reviews Data and Estimates Concern Level

An experienced toxicologist should review the predicted data and set a concern level. Following is general guidance for setting concern levels, used by EPA in screening new chemicals under TSCA:

- HIGH CONCERN
  - Evidence of adverse effects in humans
  - Conclusive evidence of severe effects in animal studies
- MODERATE CONCERN
  - Suggestive animal studies
  - Analogue data
  - Chemical class known to produce toxicity
- LOW CONCERN
  - No concern identified

ECOSAR to Estimate Aquatic Toxicity

What Does the ECOSAR Model Do?

ECOSAR (Ecological Structure Activity Relationships) estimates the aquatic toxicity of a chemicals used in industry and discharged into water. The program uses Structure Activity Relationships (SARs) to estimate a chemical's acute (short-term) toxicity and, when available, chronic (long-term or delayed) toxicity. ECOSAR can predict the potential toxicity of the chemical to plant and animal live in the water body. The model uses measured data to predict toxicity of chemicals lacking data.

How are the model predictions useful in risk assessment?

An understanding of the chemical's aquatic toxicity helps the risk assessor estimate if the release of the chemical will adversely affect aquatic biota and the aquatic ecosystem.

Inputs

CAS number or chemical structure in SMILES notation, log KOW predicted by ClogP*, and measured values for log Kow, WS, and MP should be entered if available. *ClogP predictions of log KOW should be entered because most SARs in ECOSAR were developed using KOW values predicted using ClogP. ClogP is a program developed by BioByte (www.biobyte.com). ClogP values are fairly consistent with EPI Suite™ values, however, ClogP values should be entered if available. All SARs in ECOSAR are being recalculated using EPI Suite™ log Kow values.

Outputs

Acute (48-hr or 96-hr) and Chronic (14-day, 16-day, or 30-day) values in mg/L (ppm) for fish, invertebrate (Daphnids), and green algae are provided. SAR Chemical Class is given. Log Kow cutoff values for the SARs used are provided so that the user can determine if the values are reliable. If the chemical is not soluble enough to reach effects concentrations (referred to as "No Effects at Saturation or NES") this is also indicated.

Saving Output

Results can be printed when displayed. After results are displayed click on "Save Results" and you can save results as a ".dat" file that can be opened using MSWord or WordPerfect. Output can also be copied (click on "Copy") through the Windows Clipboard. Structures can be saved as an ISIS ".skc" file or through the Windows Clipboard. Further explanations are in "Help" on the Results page.

Important Notes

- ECOSAR users should have some knowledge of environmental toxicology and organic chemistry.
- The current version of ECOSAR can not be used to estimate toxicity of certain chemical classes, for example: charged dyes, polymers, inorganics, or organometallics.
- The latest version of ECOASR – the "G" version – is incorporated into the EPI Suite™ of models.
- The "HELP" screens in ECOSAR contain useful information, including:
  - Help writing SARs
  - List of SARs programmed into ECOSAR
  - SAR equations
  - ECOSAR Chemical Class List

Where Can I Get ECOSAR?

The latest version of ECOSAR (v.099g) can be downloaded at no cost from EPA, OPPT New Chemicals Program web site: http://www.epa.gov/oppt/newchems/21ecosar.htm This version of ECOSAR has been incorporated into the EPI Suite™.

ECOSAR User Manual, "ECOSAR: A Computer Program for Estimating the Ecotoxicity of Industrial Chemicals (EPA-748-R-93-002), and Estimating Toxicity of Industrial Chemicals to Aquatic Organisms Using Structure Activity Relationships" (EPA-748-R-93-001). For a copy contact EPA's National Center for Environmental Publications and Information 800-490-9198, www.epa.gov/ncepihom/index.htm

ECOSAR to Estimate Aquatic Toxicity

Ecosar v0.99g

File Edit Functions BatchMode ShowStructure Special_Classes Help

Previous | Get User | Save User | CAS Input | Calculate

Enter SMILES: c(cccc1)(c1)C

Enter NAME: Benzene, methyl-

CAS Number: 000108-88-3

Chemical ID 1:

Chemical ID 2:

Chemical ID 3:

Log Kow: 2.540

Measured Water Sol (mg/L): 573.1

Melting Point (deg C): 25.00

Measured Log Kow: 2.730

Inputs:

CAS	108-88-3
Melting Pt	25.0
WS	573.1
Log Kow	2.540 (ClogP)
Measured Log KOW	2.73

Either the structure in SMILES or the CAS number must be entered to run the program.

Ecowin Results

Print Save Results Copy Remove Window Help

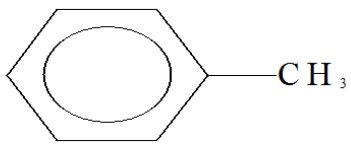
```
SMILES : c(cccc1)(c1)C
CHEM   : Benzene, methyl-
CAS Num: 000108-88-3
ChemID1:
ChemID2:
ChemID3:
MOL FOR: C7 H8
MOL WT : 92.14
Log Kow: 2.54  (User entered)
Melt Pt: 25.00 deg C
Wat Sol: 573.1 mg/L  (measured)

ECOSAR v0.99g Class(es) Found
------------------------------
Neutral Organics
```

The results may be Printed, Saved to a file, or Copied to the Windows clipboard and pasted into another Windows Program, such as MS Word.

Structure

File

The structure is shown in a separate window and can be saved as a MOL file.



Benzene, methyl-

ECOSAR Class	Organism	Duration	End Pt	mg/L (ppm)
Neutral Organic SAR (Baseline Toxicity)	: Fish	14-day	LC50	41.891
Neutral Organics	: Fish	96-hr	LC50	21.225
Neutral Organics	: Fish	14-day	LC50	41.891
Neutral Organics	: Daphnid	48-hr	LC50	23.608

ECOSAR to Estimate Aquatic Toxicity

Results from the ECOSAR Model

```
SMILES : c(cccc1)(c1)C
CHEM   : Benzene, methyl-
CAS Num: 000108-88-3
ChemID1:
ChemID2:
ChemID3:
MOL FOR: C7 H8
MOL WT : 92.14
Log Kow: 2.54   (User entered)
Melt Pt: 25.00 deg C
Wat Sol: 573.1 mg/L   (measured)

ECOSAR v0.99g Class(es) Found
Neutral Organics

                                                          Predicted
ECOSAR Class            Organism          Duration  End Pt  mg/L (ppm)
======================  ================  ========  ======  ==========
Neutral Organic SAR      : Fish            14-day    LC50       41.891
(Baseline Toxicity)

Neutral Organics         : Fish            96-hr     LC50       21.225
Neutral Organics         : Fish            14-day    LC50       41.891
Neutral Organics         : Daphnid         48-hr     LC50       23.608
Neutral Organics         : Green Algae     96-hr     EC50       15.225
Neutral Organics         : Fish            30-day    ChV         2.983
Neutral Organics         : Daphnid         16-day    EC50        1.533
Neutral Organics         : Green Algae     96-hr     ChV         2.080
Neutral Organics         : Fish   (SW)     96-hr     LC50        6.313
                           Mysid Shrimp    96-hr     LC50        4.163
                                                          mg/kg (ppm)
                                                          dry wt soil
                                                          ===========
                           Earthworm       14-day    LC50      386.488

                          tes: Chemical may not be soluble
                          e this predicted effect.
                          acute toxicity log Kow cutoff: 5.0
                          toxicity log Kow cutoff: 6.4
                          log Kow cutoff: 8.0
                    MW cutoff: 1000
```

Standard toxicity profile used by EPA for freshwater species (mg/L or ppm):

Acute effects	Duration	Endpoint
fish	96-h	LC50
daphnid	48-h	LC50
green algae	96-h	EC50
Chronic effects	**Duration**	**Endpoint**
fish	30-d	ChV
daphnid	16-d	EC50 or ChV
green algae		ChV

H-M-L Levels (mg/L or ppm)	
ACUTE	**CHRONIC**
High < 1	High < 0.1
Mod. = 1 - 100	Mod. = 0.1 - 10
Low > 100	Low > 10

These SARs are not valid ...igher ...utoff

Setting concern levels:
High Concern = Any Acute value <1 mg/L Chronic < 0.1 mg/L)
Mod. Concern = Lowest of the 3 is > 1 and < 100 mg/L (Chronic >0.1 and <10.0 mg/L)
Low = All 3 are > 100 (Chronic > 10.0 mg/L), or there are No Effects at Saturation (occurs when water solubility of the chemical is higher than an effect concentration).

Interpreting the Results from ECOSAR

Determining concern concentration (CC): CC is the lowest ChV divided by an uncertainty factor (assessment or safety factor) of 10. In order to be conservative and because the uncertainty (or assessment) factor is one significant digit, the CC will be rounded up to be one significant digit e.g., a CC of 175 will be rounded up to 200.

PBT Profiler – Estimations of Persistence, Bioaccumulation, and Toxicity

What Does the PBT Profiler Model Do?

PBT Profiler
A Component of OPPT's P2 Framework
Assessing Chemicals in the Absence of Data

The PBT Profiler is a no cost, online PBT screening methodology. It estimates environmental persistence (P), bioconcentration potential (B), and aquatic toxicity (T) of discrete chemicals based on their molecular structure. It is Internet-based and there is no cost for use. When the user accesses the PBT Profiler on the Internet, the program prompts the user to enter the CAS Registry Numbers (RNs) of chemicals under consideration. The PBT Profiler is linked to a database containing the CAS RNs and the associated chemical structures for over 100,000 discrete chemical substances. If the CAS RN is in the database, the PBT Profiler will translate the CAS RN into a chemical structure, predict the PBT characteristics, and provide a PBT profile in an easy to understand format. A drawing program is available so that the user can draw and enter the structure if the CAS RN is not in the database. The structure can also be entered as a SMILES Notation. The PBT Profiler compares the results of a profile with the PBT criteria established for Premanufacture Notices (PMNs) submitted under section 5 of TSCA; and the final rule for reporting chemicals under the Toxic Chemical Release Inventory (TRI), under section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA).

How are the model predictions useful in risk assessment?

Persistent, bioaccumulative, and toxic pollutants (PBTs) are highly toxic, long-lasting substances that can build up in the food chain to levels that are harmful to human and ecosystem health. They are associated with a range of adverse human health effects, including effects on the nervous system, reproductive and developmental problems, cancer, and genetic impacts.

Inputs

- CAS number or chemical structure in SMILES notation
- Structure can be drawn using an integrated drawing program

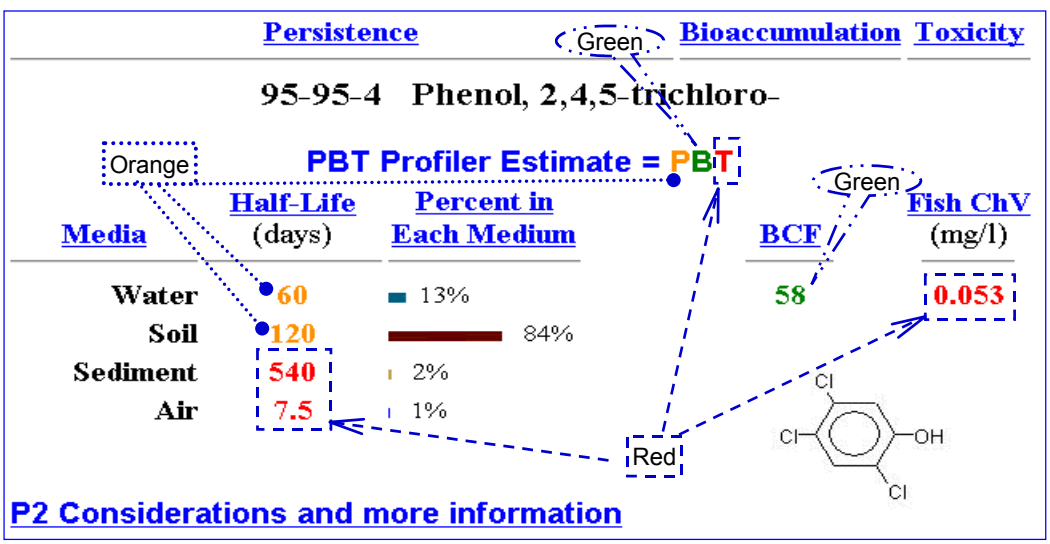
Outputs

A sample output showing the three tiers of output is provided below. Each tier increases in detail. These three levels are:

1. PBT Summary given in a color coded format, with green indicating no criteria exceeded, orange indicating criteria are exceeded, and red indicating criteria are greatly exceeded. If P, B, AND T are any combination of red or orange the chemical may be a PBT. In the example below, trichlorophenol, which is *P*BT, P is orange, B is green, and T is red, is not a potential PBT.

2. Detailed Results which gives % in each media, media half-lives; BCF; and fish chronic toxicity.

3. P2 Considerations and More Information is a link to additional detailed information on the chemicals predicted environmental fate, BCF, and toxicity that can be useful for the management of the release of the chemical to the environment and to control exposures and potential risk.



PBT Profiler – Estimations of Persistence, Bioaccumulation, and Toxicity

Examples of PBT Summary Predicted Values

CAS RN	Chemical	PBT Summary	
50-01-1	Guanidine hydrochloride	PBT	(**not** a potential PBT)
447-53-0	1,2-Dihydro-naphthalene	*PBT*	(**not** a potential PBT)
95-95-4	2,4,5-Trichloro-phenol	*PBT*	(**not** a potential PBT)
8001-35-2	Toxaphene	PBT	(a presumptive PBT*)

*Note: Toxaphene, and other chemicals is listed as PBTs in EPA's final rule on Persistent, Bioaccumulative, and Toxic Substances, are flagged by the PBT Profiler, and the user is advised that this chemical has been listed as a PBT by EPA.

Criteria Used by The PBT Profiler

Persistence and Bioaccumulation criteria are based on EPA policy statements published in the Federal Register:

- New PBT category for PMNs submitted under TSCA sec. 5
- Final rule concerning reporting under Toxics Release Inventory (TRI) under sec. 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA):
  - Adding several PBTs to the list of those requiring reporting
  - Lowering reporting thresholds for certain PBTs already on TRI.The PBT profiler uses a different set of criteria to highlight chemicals that may be toxic.

Toxicity Criteria are those used by EPA's New Chemical Program for Fish Chronic toxicity. Potential human toxicity is identified based on Chemical Categories. If the chemical being screened has structures identified and described in this document, the human health concerns of those structures are provided in the results screen.

CRITERIA used by The PBT Profiler			
PERSISTENCE	Not Persistent	Persistent	
Water, soil, sed.*	< 60 d	≥ 60 d	> 180 d
Air^	≤ 2 d	> 2 d	
BIOACCUMULATION	Not Bioaccum.	Bioaccumulative	
Fish BCF*	< 1,000	≥ 1,000	≥ 5,000
TOXICITY	Not Toxic	Toxic	
Fish ChV*	> 10 mg/L or No Effects at Saturation	10 – 0.1 mg/L	< 0.1 mg/L
EPA Criteria: *New Chemical Program, ^TRI			

Important Notes

- The PBT Profiler online site www.pbtprofiler.net provides hot links to help which explain Methodology, Criteria, Security, Interpreting Results, Examples of Chemicals to run, Chemicals that Should not be Profiled (and the reasons why these chemicals are not appropriate for the Profiler, Limitations,
- Many chemicals can be run in one session by entering the chemicals sequentially.
- For technical reasons, there are certain classes of chemicals that should not be profiled using the PBT Profiler. Check the online site for more information. The chemicals are:
  - Chemicals with Experimental Data
  - Inorganic Chemicals
  - Reactive Chemicals
  - Salts (Organic Salts)
  - High Molecular Weight Compounds
  - Chemicals with Unknown or Variable Composition
  - Mixtures
  - Surfactants
  - Highly Fluorinated Compounds

Where Can I Get The PBT Profiler?

The model can be accessed using a web browser and used online at www.epa.gov/opptintr/pbtprofiler/ The PBT Profiler can not be downloaded and used on a PC. Information on the PBT Profiler is available at www.epa.gov/opptintr/pbtprofiler/

PBT Profiler – Estimations of Persistence, Bioaccumulation, and Toxicity

Saving Output

Print Results screens on a color printer, or copy and paste ("Block", "Copy", and "Paste") into MSWord.

Sample Output From The PBT Profiler

A sample model run from the PBT Profiler of a known PBT chemical Benz a anthracene (CAS 56-55-3) is shown below printed in the color version, and in a black & white (B&W) version. Users can toggle between the color and B&W version.

The B&W version was created because not everyone has access to a color printer, and some people do have color-weak vision. Results in red (criteria greatly exceeded) in the Black & White version are **bold and underlined**. Results in orange (criteria exceeded) in the B&W version are *italicized*. Results in green (no criteria exceeded) are in normal font.